

To plan an effective program for the control of gonorrhea, more understanding is needed of the clinical course of the disease, its epidemiology, and its response to treatment.

Unknowns and Enigmas in Gonorrhea

By IRA LEO SCHAMBERG, M.D.

THE dramatic reduction in the incidence of syphilis is one of the great achievements of the last decade. Since 1947, there has been a nationwide decrease of 93 percent in reported morbidity of primary and secondary syphilis (1). The striking reduction in the number of such patients reported from public health clinics, where morbidity reporting is most complete, as well as from private physicians, suggests that this represents a real decrease in syphilis morbidity.

Gonorrhea morbidity has not followed suit, as indicated in figures 1, 2, and 3. The purpose of this paper is to present a number of unanswered questions about this ubiquitous disease. Possibly, when some of these questions have been answered we may understand why gonorrhea is reacting so differently from syphilis to modern therapeutic and public health measures.

As Babione (2) stated in 1949, "The true in-

cidence of gonorrhea in the United States is unknown and virtually unknowable." He suggested determination of the ratio of gonorrhea to syphilis, a disease for which the incidence is known with greater accuracy, as an approach to a more valid picture of the frequency of gonorrhea. In his elaborate statistical study, he computed this ratio by age in the United States Navy for 1945 and suggested that this baseline may be used in the future in estimating changes of effectiveness of control measures applied to either gonorrhea or syphilis. The increasing difference in incidence which seems to have appeared between these two diseases in recent years would appear to make this method invalid.

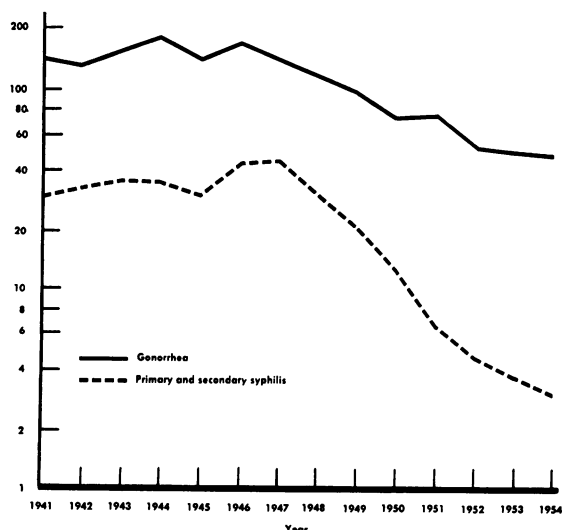
Morbidity reporting of gonorrhea among civilians has always been faulty, and conclusions drawn from such data must be made extremely cautiously. Reporting by public health clinics is a great deal more accurate than reporting by private physicians. However, patients may, for a wide variety of reasons, such as employment, economic status, or convenience, transfer from clinic to private physician or vice versa. Therefore, conclusions regarding incidence based solely on morbidity reporting from public health clinics are also open to serious error (3). Reporting by the armed services is, in all likelihood, more complete than reporting by civilians, but there are, nonetheless, many deficiencies. Evidence bearing on the incidence of gonorrhea in the United States may be summarized as follows:

1. Gonorrhea trend analyses have been made

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Figure 1. Primary and secondary syphilis and gonorrhea in the white male, 1941-54: rates per 100,000 population, continental United States.



Source: Morbidity reports, Public Health Service.

by the Venereal Disease Program of the Public Health Service (4). In reviewing data on gonorrhea cases among nonwhite males reported by clinics in 13 of the larger cities of the country during the period 1952-54, it was observed that some of the cities showed no change in numbers of cases reported; some showed a moderate increase; and some, a moderate decrease. No uniform trend was noted.

2. Analysis of the gonorrhea case rate for the United States from 1919 through 1954 (1) shows that the case rate per 100,000 population in 1954 (152) was slightly higher than in 1919 (148). The highest incidence in 1947 (284) may have been related in part to the policy of many health departments at that time of providing the then expensive penicillin free in return for morbidity reporting of venereal disease.

3. Review of venereal disease rates in the armed services reveals a decrease in syphilis (chiefly primary and secondary stages) in the Army of 85 percent, and an increase in gonorrhea of 11 percent from 1935 through 1953. In the Navy, syphilis decreased 98 percent, gonorrhea 70 percent (personal communication from the Surgeon Generals' offices, U. S. Army and U. S. Navy). The apparent decrease in gonorrhea in the Navy may be at least partly

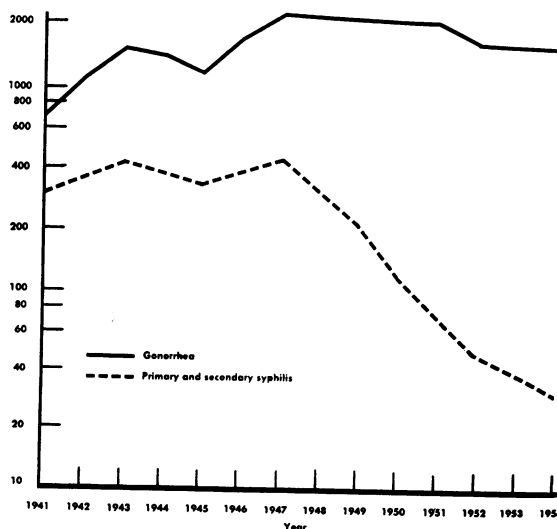
explained by the fact that the 1935 figure applied to the entire Navy, the 1953 figure only to naval personnel within the continental United States.

From these data, because of the factors mentioned above, we cannot know for certain whether gonorrhea has increased or decreased in incidence. However, it appears improbable that there has been a precipitous decline in incidence such as has occurred in early syphilis.

Many practicing physicians with whom the author has talked have expressed surprise that there is no evidence of a marked decrease in gonorrhea incidence. They state that they now see only a very few patients with gonorrhea, whereas in the past they saw many such patients. They add that complications of gonorrhea, such as arthritis and epididymitis, are now rarities. This widespread clinical impression may be at least partly explained on the following bases:

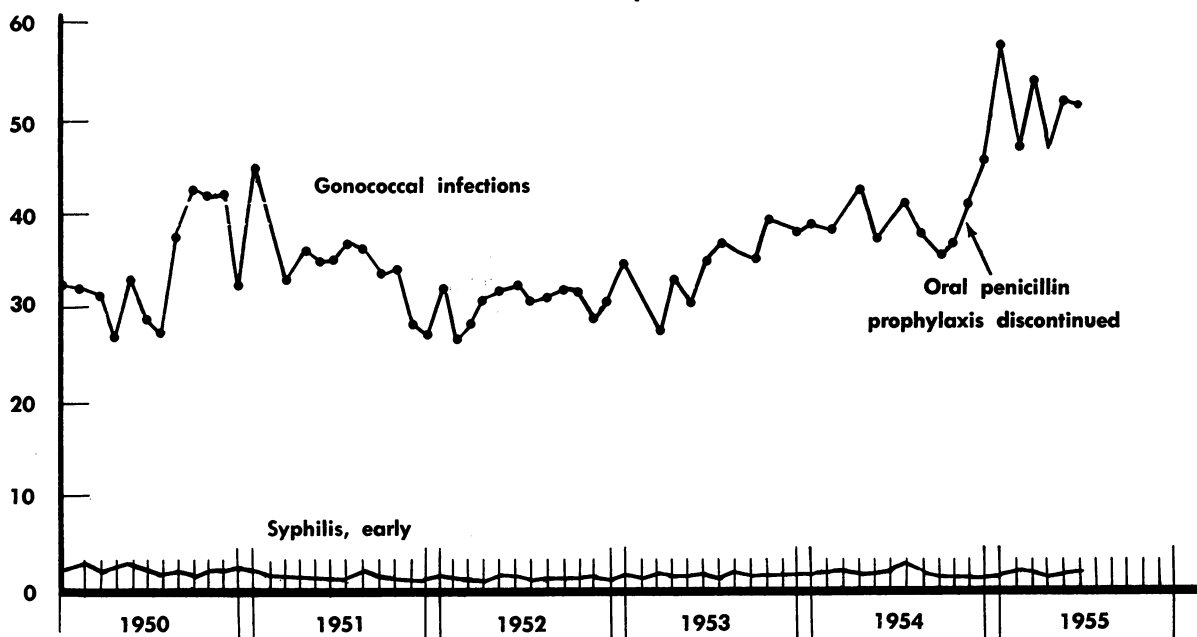
1. In the presulfonamide days (before 1937), all types of gonorrhea persisted over a period of weeks or months. If one may estimate that in those days the average male patient with gonorrhea visited a clinic or physician 3 times a week for 3 months, he would have been seen approximately 40 times. Today, the male patient with gonorrhea need be seen only once to

Figure 2. Primary and secondary syphilis and gonorrhea in the nonwhite male, 1941-54: rates per 100,000 population, continental United States.



Source: Morbidity reports, Public Health Service.

Figure 3. Syphilis and gonorrhea in United States Navy and Marine Corps, 1950-55: annual incidence rates per 1,000.



Source: *Stat Navy Med* July 1953 September 1955.

receive his curative injection of penicillin. This sharp decrease in the number of times patients with gonorrhea are now seen might be interpreted by the physician as a decrease in incidence.

2. Every general practitioner today is able to cure gonorrhea promptly. Therefore, many patients who previously were referred to clinics and specialists are now being seen only by the general practitioner.

3. A change in the character of gonorrhea in the course of the past 20 years may partly explain the great decrease in complications of gonorrhea.

4. Another explanation may be that the majority of individuals infected with gonorrhea are treated relatively early with penicillin, which prevents the development of complications.

It is probable that intensive public health control measures plus widespread use of penicillin for diseases other than syphilis are the factors chiefly responsible for the dramatic decline in syphilis. One would think that gonorrhea would be more susceptible to these measures than is syphilis. In the male, the incubation period is short, permitting time for in-

fection of few sexual contacts before symptoms appear, and symptoms usually bring the patient promptly to medical care. Transmission almost solely by sexual contact limits the number of exposed individuals. Penicillin cures rapidly and makes the patient noninfectious. In addition, for the past 2 years in many areas of the country, public health measures to achieve prompt treatment of female contacts have been carried out.

On the other hand, the brief incubation period can favor the spread of gonorrhea, as has been pointed out by Magnuson in a personal communication. Penicillin given fortuitously for an unrelated condition must be given during the incubation period of gonorrhea if it is to curb infectiousness more rapidly than will penicillin given for the disease itself. It is less likely that penicillin will be received coincidentally during a brief incubation period than during a long one.

The following questions come to mind.

Q. Does penicillin cure gonorrhea?

A. Love and Finland (5) have recently shown that the gonococcus has not developed resistance to penicillin in vitro in the period 1945-54. However, there is evidence that some or-

ganisms are most sensitive to penicillin when actively metabolizing and are significantly more resistant when in a quiescent state (6). Rees (7) states, "When the gonococcus lies in a closed or intermittently draining focus, it may escape the action of penicillin, and is a potential source of reinfection if the focus is reopened." "Failure" of penicillin to cure gonorrhea has been reported by a number of authors (8-13), and may usually be explained by one of the following factors:

1. Reinfection.
2. Inadequate dosage.
3. Destruction of penicillin by penicillinase.
4. Resistance of inactive gonococci in an unfavorable environment (6).

5. Too brief blood level (aqueous penicillin, exertion, hyperemia of depot, low renal threshold, and so forth).

6. Misdiagnosis (nonspecific urethritis, and so forth).

Q. How long is gonorrhea infectious in the untreated female?

A. No evidence is available, in view of the impossibility of differentiating persistence of infection from reinfection.

Q. What factors cause or favor development of gonorrheal pelvic inflammatory diseases (PID)?

A. Some theories, no factual knowledge.

Q. What percentage of infected females develop PID?

A. Lewis (14) believes that many escape.

Q. What is the time interval from infection to PID?

A. Wertheim, as quoted by Peters (15), is said to have found gonococci in the endometrium 5 to 14 days after sex contact. There are many conjectures, but no knowledge.

Q. In the woman with PID does a positive cervical or urethral culture result from the original infection which caused the PID or from more recent superinfection?

A. No data, but in view of the lack of immunity resulting from gonorrheal infection and difficulty in culturing gonococci in women with PID of long duration, the latter appears probable.

Q. Is the patient with PID infectious?

A. In a study of sexual contacts of men with gonorrhea, Goldstein (16) found positive cervical cultures in 35 percent of the women who had PID and in only 21 percent of those found free of PID (table 1).

Q. Are women with repeatedly negative cultures necessarily free of infection and noninfectious?

A. Lewis (14) and Rees (7) believe that intermittently draining cervical glands may permit a woman to be infectious from time to time despite repeated negative cultures. The male urethra may also be a more efficient sampler and culture medium than are the physician's swab and the bacteriologist's petri dish. Koch (17) found, in women with gonorrheal cervicitis, alkaline cervical mucus and a high percentage of positive gonorrhea cultures in the first half of the menstrual cycle, acid cervical mucus and few positive cultures from the 22d to the 25th day (table 1). Therefore, negative cultures late in the menstrual cycle would appear to give no assurance of freedom from infection.

Q. In the female, can persistence of gonorrheal infection, relapse, reinfection, and superinfection be differentiated?

A. To date, no.

Q. Does penicillinase inactivate penicillin locally and prevent cure of gonorrheal proctitis?

A. Hagerman (18) found a higher relapse rate in women with proctitis and suggested that penicillinase (produced by *Bacterium coli*) inactivates penicillin in the rectum. However, Bang (19) found no evidence to support this thesis. Many bacteria produce penicillinase, an enzyme which destroys the antibacterial action of penicillin, and Tacking (20) has shown that secondary infection by one of these bacteria may inhibit the action of penicillin against pathogenic penicillin sensitive organisms in vivo.

Q. How can the effect of an intensive public health attack on gonorrhea be evaluated?

A. Greenberg and Mattison (21) have emphasized the importance of program evaluation and give examples of intermediate and ultimate objectives that may be used. The attack rates of urethritis in the male and of pelvic inflammatory disease in the female appear to be our best measuring rods.

Table 1. Gonorrhea cultures in women

Source of culture and author	Year	Type of patient	Number of women	Percent positive
Cervix:				
Davidson and Shepard (32)-----	1948	Named sex contacts of males with gonorrhea----	42	34
Goldstein (16)-----	1955	do-----	538	21
Somerson et al. (37)-----	1955	do-----	86	47
Cohn (28)-----	1944	"Suggestive history or suspicious symptoms of GC."-----	230	36
Cooke and Lankford (33)-----	1945	Obstetrics and gynecology clinic-----	2,000	23
Morton (37)-----	1945	Young women apprehended on morals charges-----	over 500	about 25
Peters (15)-----	1947	Gynecology clinic-----	2,832	14
Koch (17)-----	1947	6-16 days postmenstrual-----	14	96
		22-25 days postmenstrual-----	4	0
Goldstein (16)-----	1955	Named sex contacts with PID ³ -----	49	35
Urethra:				
Cohn (28)-----	1944	"Suggestive history or suspicious symptoms of GC."-----	230	18
Rectum:				
Bang (19)-----	1954	"Women with gonorrhea"-----	428	25
Fallopian tubes:				
Menge (34)-----	1897	PID-----	106	22
Hyde (34)-----		do-----	2,973	19
Andrews (34)-----		do-----	634	22
Curtis (31)-----	1921	PID with gross evidence of active inflammation-----	64	30
		PID without gross evidence of active inflammation-----	128	0
Studdiford (35)-----	1938	PID-----	24	67
Cohn (28)-----	1944	PID (7 treated with sulfa)-----	19	0
Intra-abdominal fluid:				
Vermeeren and TeLinde (36)---	1954	Ruptured pelvic abscesses-----	21	0

¹ 25 cultures. ² 16 cultures. ³ Pelvic inflammatory disease.

Q. Has the attack rate of urethritis in the male and pelvic inflammatory disease in the female been reduced?

A. No evidence has been found for a drop in PID, but Lee (22) has shown a decrease in urethritis in the male in a rural area adjacent to a military installation during an intensive cam-

paign (table 2). Pereyra and his co-workers (3) have carried out a most interesting study in Atlanta, Ga. During an intensive 1½-year campaign, the number of nonwhite male patients applying to the health department clinic with gonorrhea has remained approximately constant. However, 15 Negro physicians practicing in the area stated on interview that they had experienced a 77-percent decrease in gonorrhea in males in their offices from 1952 through 1954. In addition, many clinic patients interviewed in 1955 stated that they had previously received treatment for gonorrhea from a private physician. The authors conclude that a shift of patients from private to clinic care conceals an actual decrease in gonorrhea incidence.

Q. What percentage of men sexually exposed to women with infectious gonorrhea acquire infection?

A. Certainly not all of them (personal communication from E. W. Thomas).

Q. Why do some escape?

A. May it be related to the length of the

Table 2. Effect of vigorous campaign against gonorrhea in an area near a large Army camp¹

Date	Morbidity (in males)	
	Civilian (number of cases)	Military (rate per 1,000)
January-June 1951 ² -----	444	270
July-December 1951 ³ -----	398	201
January-June 1952 ⁴ -----	304	162

¹ Lee, S. S.: Gonorrhea control measures—A study in New Hanover County, N. C. Pub. Health Rep. 69: 998-1007, October 1954.

² 6 months prior to campaign.

³ First 6 months of campaign.

⁴ Second 6 months of campaign.

urethra distal to the fossa navicularis? (Personal communication from P. Pelouze.)

Q. Is nongonococcal urethritis a venereal disease?

A. This condition is probably not a single entity, but in different patients may be due to mechanical, chemical, toxic, infectious, or psychosomatic factors, individually or in combination. Certain types may be transmitted by sexual intercourse.

Q. Does the gonococcus transmute into pleuropneumonia-like organisms (PPLO) under adverse conditions, and thereby become penicillin resistant?

A. Pleuropneumonia-like organisms cause certain animal diseases (bovine pleuropneumonia, agalactia in sheep and goats, polyarthritis in rats) and are found in normal humans in the female genital tract, throat, and saliva.

These organisms are resistant to all antibiotics except streptomycin.

They have been grown from cultures of eight different bacteria (including the gonococcus) when penicillin is added to solid culture media.

On transfer to fluid media, PPLO from *Streptobacillus moniliformis*, *Proteus*, and *Bacteroides* revert to original form; from other organisms, PPLO fails to grow. (PPLO isolated from animals and humans grow well in fluid media.)

Two theories may explain these phenomena: (a) symbiotic or accidental association of PPLO with bacteria; (b) growth phase—bacteria change to PPLO form under adverse conditions and thereby become penicillin resistant (23-27).

Q. Why is so little research in gonorrhea being carried out in this country? A search of the recent literature reveals significantly more investigative work on gonorrhea in the Scandinavian countries, Germany, Russia, and Great Britain than in the United States.

A. Reasons for this lack of research in the United States are not known.

How may we in the future learn the answers to some of these questions?

1. Better diagnostic tools might be developed, such as more sensitive cultural methods. Cohn and Grunstein (28) and Schauffler (personal communication) consider gonococcus culture an

insensitive method, in that many organisms must be inoculated in order to get growth. Another tool would be sensitive and specific serologic, skin, or other tests.

2. Repeated examination of women in a protected environment, following natural or purposeful infection, in order to observe the natural course of the disease and response to treatment. Such studies have been carried out in syphilis (29) and in gonorrhea in the male (30), and are equally permissible, feasible, and potentially valuable in gonorrhea in the female.

3. Repeated urethral and cervical cultures from women scheduled for hysterectomy. After operation, cultures from the excised cervix utilizing the following methods and materials: micropipette aspiration of cervical glands under the dissecting microscope, scraping of multiple cut surfaces, groundup pieces of tissue, and pus and exudate. Sensitivity of cultures would be greatly enhanced under these conditions.

4. After baseline studies of untreated women, similar studies on women treated with penicillin should help to answer the question whether penicillin cures gonorrhea in the female.

5. Similar studies in women with pelvic inflammatory disease scheduled for laparotomy. In the era of surgical treatment for PID, bacteriological studies at operation provided interesting data. Curtis (31) in 1921 reported on bacteriological study of fallopian tubes from 192 patients. The gonococcus was found in 30 percent of tubes showing gross evidence of active inflammation but was found in no case in which the tubes were grossly negative, even when there was histological evidence of active inflammation. Curtis stated that it is only rarely possible to obtain viable gonococci from patients who have been free from fever and leucocytosis for more than 10 days to 2 weeks. He concluded that the gonococcus lives only a short time in the tube, and that persistently or recurrently active gonorrheal salpingitis is due either to recurrence of infection from without (reinfection) or to repeated invasion of bacteria from the chronically infected lower genital tract. Such studies should be repeated using the most sensitive present-day cultural methods.

Conclusions

1. The true incidence of gonorrhea in the United States is unknown.

2. Widespread use of antibiotics and intensive control measures have reduced the attack rate of syphilis 93 percent in the past 8 years. It is unlikely that gonorrhea has declined to a similar extent.

3. The reasons for this difference in response to treatment are not known.

4. Interest in research in gonorrhea is at an all time low in this country.

5. To gain the knowledge needed to press the battle against the gonococcus, there must be a reawakening of interest in gonorrhea among research workers, as well as among those who provide the funds.

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CDC Laboratory Refresher Training Courses

The Communicable Disease Center of the Public Health Service will give its annual laboratory refresher training courses in Chamblee, Ga., July 1956 through June 1957, according to the following schedule:

Laboratory methods in the diagnosis of bacterial diseases:

- Part 1. General bacteriology. September 10-21.
- Part 2. General bacteriology. September 24-October 5.
- Enteric bacteriology. October 8-19.

Laboratory methods in the diagnosis of parasitic diseases:

- Part 1. Intestinal parasites. September 10-October 5.
- Part 2. Blood parasites. October 8-26.

Laboratory methods in the diagnosis of viral and rickettsial diseases. October 15-26.

Laboratory methods in the diagnosis of rabies. October 29-November 2.

Laboratory methods in medical mycology:

- Part 1. Cutaneous pathogenic fungi. January 7-18.
- Part 2. Subcutaneous and systemic fungi. (Completion of part 1 or the equivalent education or experience is a prerequisite.) January 21-February 1.

Laboratory methods in the diagnosis of tuberculosis. January 21-February 1.

Laboratory methods in the study of pulmonary mycoses. February 4-15.

Laboratory diagnostic methods in veterinary mycology. February 25-March 1.

Laboratory methods in the diagnosis of viral and rickettsial diseases. March 11-22.

Serologic methods in the diagnosis of parasitic and mycotic infections. March 11-22.

Laboratory methods in the diagnosis of rabies. March 25-29.

By special arrangement the following courses will be offered:

- Laboratory methods in the diagnosis of malaria.
- Virus isolation and identification techniques.
- Typing of *Corynebacterium diphtheriae*.
- Special problems in enteric bacteriology.
- Phage typing of *Salmonella typhosa*.
- Laboratory methods in diagnosis of leptospirosis.
- Serologic differentiation of streptococci.

Information and application forms should be requested from Laboratory Training Services, Communicable Disease Center, Public Health Service, P. O. Box 185, Chamblee, Ga.